

DEPARTMENT OF HEALTH AND HUMAN SERVICES

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Food and Drug Administration

21 CFR Part 312

[Docket No. 97N-0030]

Investigational New Drug Applications; Amendment to Clinical Hold Regulations for Products Intended for Life-Threatening Diseases and Conditions

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending the regulations governing investigational new drug applications (IND's) to permit FDA to place a clinical hold on one or more studies under an IND involving a drug that is intended to treat a life-threatening disease or condition affecting both genders. The amendments permit the agency to place a clinical hold on such studies if *men or women* with reproductive potential who have the disease or condition are otherwise eligible but are categorically excluded from participation solely because of a perceived risk or potential risk of reproductive or developmental toxicity from use of the investigational drug. This rule was developed in response to the past practice of excluding women with reproductive potential from early clinical trials because of a perceived risk or potential risk of reproductive or developmental toxicity. The final rule does not impose requirements to enroll or recruit a specific number of men or women with reproductive potential.

DATES: The regulation is effective [insert date 60 days after date of publication in the **Federal Register**].

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SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of September 24, 1997 (62 FR 49946), FDA proposed to amend its regulations in § 312.42 (21 CFR 312.42) governing clinical holds. A clinical hold is an order that FDA may issue to a sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation for the development of a new drug or biological product (§ 312.42(a)). Under the proposed amendments, FDA could impose a clinical hold on any proposed or ongoing clinical trial for a life-threatening disease or condition that affects both genders if men or women with reproductive potential who have the disease or condition being studied were excluded from eligibility in any phase of the clinical investigation solely because of a risk or potential risk of reproductive toxicity or developmental toxicity from use of the investigational drug. As explained in the preamble to the proposed rule (62 FR 49946 at 49947), the amendments address the exclusion from clinical trials of members of either gender who have a life-threatening disease or condition. Because such exclusions have in the past been applied primarily to women, however, it is expected that the impact of the amendments will be to ensure that women who have a life-threatening disease or condition are not categorically excluded from investigational trials of drug products for that disease or condition solely because of a perceived risk or potential risk of reproductive or developmental toxicity from the use of the investigational drug. FDA provided 90 days for public comment on the proposed rule.

II. Description of the Final Rule

FDA regulations identify the grounds for placing a clinical hold on proposed or ongoing phase 1 studies (§ 312.42(b)(1)) and on proposed or ongoing phase 2 or phase 3 studies (§ 312.42(b)(2)).

FDA is amending these clinical hold regulations to provide an additional ground for placing a phase 1, phase 2, or phase 3 study on clinical hold. Under these amendments, FDA may impose a clinical hold on any proposed or ongoing clinical trial for a life-threatening disease or condition that affects both genders if men or women with reproductive potential who have the disease being studied are excluded from eligibility in any phase of the investigation because of a risk or potential risk of reproductive or developmental toxicity from use of the investigational drug.

The proposed rule refers to studies under an IND involving a drug that is intended to treat a life-threatening illness or disease affecting both genders. As stated in the proposal (62 FR 49946 at 49951), the definition of life-threatening illness or disease is intended to be consistent with the agency's IND regulations (§ 312.81(a)(1)). Under the IND regulations, the term life-threatening is applied to "conditions" or "diseases." To remain consistent with current terminology, the agency is amending the final rule to refer to "life-threatening diseases or conditions."

The clinical hold under these amendments would not apply to clinical studies conducted under special circumstances, such as studies pertinent to only one gender (e.g., to evaluate the excretion of a drug in semen or its effects on menstrual function).

As described in the proposed rule, a clinical hold would not be applied to a clinical study conducted in men, as long as a study that does not exclude subjects with reproductive potential has been planned or is being conducted in women. The agency expects that in an active IND, studies that do not exclude women or men with reproductive potential will be underway or will commence in a timely manner. To clarify this expectation, the final rule has been modified to state that a clinical hold would not be ordered for a study conducted only in men or only in women, as long as a study that does not exclude members of the other gender with reproductive potential is being conducted concurrently or will take place within a reasonable time agreed upon by the agency (§ 312.42(b)(1)(v)(B)). FDA expects that a discussion between the sponsor and the agency concerning a reasonable time for carrying out the study would take place at a pre-IND meeting or with the submission of the IND.

As stated in the proposed rule, this amendment to the IND regulations would not apply to clinical studies conducted exclusively in healthy volunteers (62 FR 49946 at 49951). The final rule has been modified in § 312.42(b)(1)(v) by adding paragraph (C) to clarify that the rule applies to clinical investigations that are conducted only in subjects who have the disease or condition that the drug is intended to treat.

III. Comments on the Proposed Rule

FDA received 26 letters, including letters from manufacturers, individuals, advocacy groups, and trade associations, commenting on the proposed rule. The majority of comments supported FDA's proposal to prohibit the exclusion of women from investigational studies through the clinical hold mechanism. Many comments suggested changes that would have narrowed or broadened the proposal.

A. General Comments

1. Several comments indicated that if women with reproductive potential are capable of acquiring a disease, such women should be included in clinical trials regardless of their ability to become pregnant. Many comments stated that FDA's goal of ensuring that women with reproductive potential who have a life-threatening disease are not categorically excluded from trials in the future is "an unassailable position." Another comment strongly recommended that FDA finalize the proposed rule, noting that despite FDA's 1993 "Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs," there has been little improvement in opening enrollments (especially in phase 1 and phase 2 trials) to fertile women and in increasing enrollment of women overall. The agency agrees with these comments.

2. One comment stated that women of reproductive age with life-threatening diseases who are fully informed should be included in all stages of product development. The same comment urged FDA to closely monitor the implementation of the new rule and to continue the development of policies that would minimize risks while allowing productive research on women and men.

FDA will monitor the implementation of this final rule as part of the general IND process and will continue to encourage research on the treatment and prevention of diseases and conditions in all individuals.

B. Applicability/Scope of the Proposed Rule

3. Section 312.42(a) states that “[w]hen an ongoing study is placed on a clinical hold, * * * patients already in the study should be taken off therapy involving the investigational drug unless specifically permitted by FDA in the interest of patient safety.” One comment noted that FDA did not define “patient safety” in the preamble to the proposed rule. The comment requested that the agency consider indirect harm to patients in an evaluation of whether continuation of therapy involving an investigational drug is in the interest of patient safety.

Generally, studies are placed on clinical hold because FDA considers it unsafe to carry the studies forward. In the present case, the hold does not imply such a conclusion. FDA generally intends to place trials that inappropriately exclude individuals with reproductive potential on hold at the time of protocol submission. However, if a trial that has begun is placed on clinical hold under this rule, it usually should not be necessary to stop an individual subject’s treatment.

4. Three comments discussed the definition of the term “life-threatening.” Two comments expressed concern that the definition could be construed to include acute and chronic illnesses, such as status asthmaticus, epilepticus, anaphylaxis, diabetes, hypertension, and severe hypercholesterolemia. One proposed narrowing the definition to encompass only those diseases identified in the proposed rule as being of concern to FDA. The third comment suggested broadening the definition to include chronic conditions such as epilepsy.

The definition of life-threatening is not intended to be limited to only those diseases and conditions where death is imminent, or broad enough to include acute or chronic diseases where death from the disease or condition is unlikely. The definition of life-threatening encompasses any disease or condition where the likelihood of death is high unless the course of the disease is interrupted. This rule is grounded in FDA’s belief that people who are suffering from a disease

or condition that is life-threatening despite available therapy should have an opportunity to participate in a clinical trial intended to address the disease or condition. Although many acute and chronic illnesses are adequately controlled by existing therapies, some of these illnesses may have stages or aspects that continue to carry a high likelihood of death despite existing therapies. Such a condition or disease would be considered life-threatening within the meaning of this rule.

5. The agency received two comments addressing the need to balance access to investigational drugs and risks to study participants. One comment stated that while risks can be minimized through mechanisms such as informed consent and study design, the rule needs to be sufficiently flexible to address exceptional circumstances where potential risks of a drug may outweigh the potential benefit. Another comment stated that balancing the need for access to investigational drugs and minimizing patient risk would be better served by data-driven dialogue between sponsors and FDA than by the rule.

The agency acknowledges that balancing access and patient risk is complex and that the specific circumstances of the trial may be pertinent. Physicians and patients are generally willing to accept greater risks from use of medical products that treat life-threatening diseases or conditions than they would accept from those that treat less serious conditions (53 FR 41516 at 41518, October 21, 1988; 62 FR 49946 at 49949). Nonetheless, institutional review boards (IRB's) must still determine that risks to study participants are minimized by the use of procedures consistent with sound research design and that the risks to study participants are reasonable in relation to anticipated benefits (21 CFR 56.111(a)(1) and (a)(2)).

FDA provides frequent opportunities for sponsors to meet with the agency to discuss the details of clinical investigations. For example, the clinical hold regulations specifically encourage discussion about deficiencies in an investigation. FDA will attempt to discuss and satisfactorily resolve the matter with the sponsor before issuing the clinical hold order (§ 312.42(c)). As stated in the proposed rule, a study would be placed on clinical hold only as a last resort (62 FR 49946 at 49953).

6. The agency received divergent comments about the scope of the rule. Two comments stated that FDA should expand the regulation to include all clinical trials.

The agency declines the suggestion to expand the scope of the regulation to include all trials. At this time, there is an ethical basis for seeking to ensure that women with reproductive potential are not categorically excluded from trials of products being developed to treat life-threatening diseases and conditions. As discussed in the preamble to the proposed rule (62 FR 49946 at 49949), FDA has concluded that all trials involving patients with life-threatening diseases or conditions should, for the purposes of the rule, be considered to have therapeutic benefit. The ethical principle of justice does not support categorical exclusion of one group that might benefit from participation in clinical research for life-threatening diseases and conditions. Although similar considerations might apply to all human drug trials, the agency recognizes that the potential detriment of being excluded from a trial is greater when the subjects have life-threatening diseases or conditions.

7. One comment stated that because all new drugs are potentially teratogenic, FDA should not permit administration of any drug to women with reproductive potential until there is evidence of general safety and effectiveness from phase 1 and phase 2 trials.

Although a risk or potential risk of developmental toxicity might exist from participation in a study, benefits that might accrue to a woman with reproductive potential who has the life-threatening disease or condition could outweigh such a risk. Furthermore, such risks can be reduced or eliminated (62 FR 49946 at 49949).

The risk of fetal exposure is eliminated by preventing pregnancy. Sponsors and IRB's can require the use of pregnancy testing to detect unsuspected pregnancy prior to initiation of study treatment and at intervals during the course of drug exposure. When the study design permits, sponsors can minimize potential fetal exposure in the short term by timing studies to coincide with the early follicular phase of the menstrual cycle. Women and men can eliminate the possibility of pregnancy through abstinence and can reduce the possibility of pregnancy through the use of one or more methods of contraception for the duration of drug exposure (62 FR 49946 at 49950).

The agency finds that exclusion of women from early trials is not medically necessary because the risk of fetal exposure can be minimized. Initial determinations about whether the risk is adequately addressed are properly left to patients, physicians, local IRB's, and sponsors, with appropriate review and guidance by FDA (58 FR 39406 at 39408, July 22, 1993).

8. The agency received multiple comments stating that historically, IRB's have been a source of exclusionary policies without scientific justification, and FDA needs to be active in ensuring that IRB's do not wrongly exclude women with reproductive potential. One comment suggested that FDA adopt new procedures to carefully monitor IRB's and encouraged quick enforcement of this rule if women with reproductive potential are inappropriately excluded.

Initial determinations about risk and other aspects of the safety of proposed investigations are properly left to patients, physicians, sponsors, and local IRB's with appropriate review and guidance by FDA (58 FR 39408). FDA has established procedures for IRB's at part 56 (21 CFR part 56). Although IRB's play a role in the determination of eligibility criteria for investigations, FDA plans to ensure compliance with this rule primarily through review of IND submissions for drugs that are intended to treat life-threatening diseases and conditions. If the agency makes an initial determination that unwarranted restrictions were placed on the eligibility of women, FDA will attempt to discuss and satisfactorily resolve the matter with the sponsor prior to issuing the clinical hold order (§ 312.42(c)). If a satisfactory resolution cannot be found, an IND may be placed on clinical hold.

9. Another comment recommended that FDA encourage trial sponsors and IRB's to broadly interpret "de facto exclusion" to avoid unnecessarily excluding women with reproductive potential.

The exclusion of subjects with reproductive potential addressed by this rule includes both explicit exclusion and de facto exclusion. De facto exclusion would result from study criteria that are not essential to accomplish the goals of the study and that have the effect of precluding enrollment of participants with reproductive potential (e.g., requiring sterilization or requiring weight or other physical characteristics).

10. Two comments suggested that the agency strengthen its policies by requiring that data collected under IND's be analyzed by gender.

The suggestions are outside the scope of this rulemaking, but in the **Federal Register** of February 11, 1998 (63 FR 6854), FDA issued the demographic subgroup rule, which revised new drug application (NDA) content and format regulations at 21 CFR 314.50(d)(5). The regulation requires that effectiveness and safety data be presented in each NDA for demographic subgroups, including gender subgroups. This regulation will ensure that data collected under IND's and submitted to the agency will be analyzed by gender.

11. Many comments expressed disappointment that the proposed rule did not contain requirements to enroll or recruit a significant number of women with reproductive potential in clinical trials. Several other comments misunderstood the intent of the rule and questioned its adequacy in ensuring appropriate enrollment and retention of women in trials. An additional comment stated that the proposed rule did not address requirements for appropriate recruitment strategies to ensure that low-income women are represented in clinical trials.

As stated in the preamble to the proposed rule, the primary goal of the rule is to ensure that women with reproductive potential who have a life-threatening disease or condition are not categorically excluded from participation in clinical investigations because of their reproductive capacity (62 FR 49946 at 49947). This rule is thus concerned with eligibility criteria for individual studies. Issues related to the enrollment of significant numbers of women with reproductive potential in clinical trials are under consideration by the agency.

The demographic subgroup rule also includes a requirement (21 CFR 312.33(a)(2)) that IND annual reports provide demographic data on subjects of trials. Although the demographic subgroup rule does not require the inclusion of a particular number of individuals from specific subgroups, it will further focus sponsors' attention throughout the drug development process on clinical trial enrollment. The demographic subgroup rule should also help sponsors better evaluate in their applications the safety and efficacy profiles of drugs for various subgroups, including gender.

12. The agency received one comment stating that pregnant women have the same right to make informed decisions about their own treatment as other women with reproductive potential. The comment concluded by recommending that the proposed regulation also apply if pregnant women are excluded from clinical trials for life-threatening diseases.

For the purpose of this rulemaking, FDA does not intend the phrase “women with reproductive potential” to include pregnant women (62 FR 49946 at 49947). The agency does not question the ability of pregnant women to provide informed consent. There is, however, increased complexity in conducting clinical trials with pregnant women because of their changing physiology. FDA will continue to explore this issue in other forums.

13. One comment recommended that the final rule clearly state that it applies to the exclusion of men in clinical trials and that the agency will carefully monitor the use of the clinical hold in studies that exclude men.

As explained in the preamble to the proposed rule, although men have rarely been excluded from studies because of reproductive potential, the rule addresses the exclusion from clinical trials of members of either gender who have a life-threatening disease (62 FR 49946 at 49947). Section 312.42(b)(1)(v) and (b)(2)(i) state that FDA may place any phase of a proposed or ongoing investigation on clinical hold if

[t]he IND is for the study of an investigational drug intended to treat a life-threatening disease or condition that affects both genders, and *men or women* with reproductive potential who have the disease being studied are excluded from eligibility in any phase of clinical investigation because of a risk or potential risk of reproductive * * * or developmental * * * toxicity * * *.

(emphasis added). As part of the IND process, FDA reviews protocol inclusion and exclusion criteria, including gender-related eligibility.

14. In the preamble to the proposed rule, the agency stated that it is important for potential study participants to be provided with an opportunity to discuss their involvement in a clinical trial with their sexual partner. FDA further stated that when deciding whether to participate in

a clinical trial for an investigational drug, potential participants should be able to weigh the potential risks of their participation in consultation with their spouse or partner, their health care provider, and their researcher (62 FR 49946 at 49950). Two comments expressed concern that these statements could be construed to mean that such consultation with a partner must occur prior to enrollment. One comment indicated that many women are not sufficiently empowered to resist intimidation by their partner to make an independent decision if their partner agrees or disagrees with participation in a clinical trial. The second comment indicated that not all potential participants have one sexual partner and that no one should be excluded from participating in a clinical trial because of multiple sexual partners. This comment also indicated that women who are unable to negotiate the terms of sexual behavior or the cooperation of their partner(s) with contraceptives should not be categorically excluded from participation in clinical trials.

Women and men can eliminate the possibility of pregnancy through abstinence and can reduce the possibility of pregnancy through the use of contraception for the duration of drug exposure, which may exceed the length of the clinical trial. The cooperation of an individual's sexual partner(s) may be needed to ensure that abstinence occurs or that appropriate contraceptive methods are used, but such cooperation is not always essential. Potential participants should be able to make autonomous decisions about contraception. Potential study participants should discuss with investigators their ability to maintain adequate contraception prior to determining whether they should participate in the study. The rule is not intended to ignore the risks associated with an unintended pregnancy, including the potential for developmental toxicity; rather it is based on the view that IRB's, investigators, and subjects can manage those risks.

Risks to participants in early clinical trials can also be reduced through the proper use of the informed consent process. Potential participants who are heterosexually active must be aware of the need to ensure that appropriate contraceptive measures are taken to prevent pregnancy and of any additional risks in the event of pregnancy. While individuals should be encouraged to involve

their sexual partner(s) in their decisionmaking process, the ultimate decision concerning whether to volunteer for a clinical trial should rest with the individual.

C. Reduction of Risks to Participants

15. The agency received several comments on the discussion of the informed consent process in the preamble to the proposed rule. The majority of comments concerning informed consent supported the agency's reliance on this process and other mechanisms to protect participants in early clinical trials. Two comments stated that the informed consent process may encourage potential study participants to act responsibly and make their own risk-benefit analysis. One comment stated that participants need to be adequately informed about available information and about areas in which data are lacking. Two other comments noted the importance of animal reproductive toxicity studies and the inclusion of information obtained as a result of such studies in the informed consent process.

There are a number of mechanisms, including the proper use of informed consent, to protect participants in clinical trials. Sponsors, investigators, and IRB's have responsibility for ensuring participant safety and protecting the rights of participants. FDA's informed consent regulations require that potential study participants be adequately informed that the study involves research, that there may be foreseeable risks or discomforts, and that there may be unforeseeable risks, such as potential risks to the embryo or fetus if a female study participant becomes pregnant (§ 50.25(b)(1) (21 CFR 50.25)(b)(1)). The existence of appropriate alternative procedures or courses of treatment, if any, must also be disclosed to the potential study participant (§ 50.25(a)(4)). Any reasonably foreseeable risks to the participant shown from the results of completed animal reproductive toxicity studies must be discussed in informed consent. When preclinical teratology and reproductive toxicity studies are not completed prior to the initial studies in humans, male and female study subjects should be informed about the lack of full characterization of the test article as well as the potential and unknown effects of the test agent on conception and fetal development. All study subjects should be provided with new pertinent information arising from

preclinical studies as it becomes available, and informed consent documents should be updated when appropriate. If there is no relevant information, the informed consent should explicitly state this fact and should indicate the risks that cannot be ruled out.

16. The agency stated in the preamble to the proposed rule (62 FR 49946 at 49950) that when the teratogenic effects of a drug are well established, the agency, sponsor, or IRB may require the use of contraception to prevent pregnancy in sexually active individuals with reproductive potential. One comment noted this statement and suggested that the regulation clearly state that all women in all clinical trials have the right to be fully informed and to balance the risks and benefits of participation.

In most circumstances, a study protocol does not need to require specific contraceptive approaches. In accordance with good medical practice, it is expected that volunteers in clinical trials will take appropriate precautions against becoming pregnant. The agency, sponsor, or IRB may require that a protocol provide for instructions to the volunteer about effective measures to avoid pregnancy. Other appropriate precautions include efforts to ensure that a woman volunteer is not pregnant at the time a trial begins, such as pregnancy testing to detect the beta subunit of the human chorionic gonadotropin molecule. Pregnancy testing may need to continue during the trial and after the drug administration portion of the trial has ended, based on the half-life of the drug under study and other considerations. Contraceptive counseling by a qualified health care provider should be offered and provided to trial participants with a focus on the use of highly effective contraception, allowing for abstinence if a woman has successfully used that as her chosen method of birth control. Although women retain control over their reproductive decisions, women and the investigator should consider together the benefits and risks of participation, including the risks resulting from an inability to maintain adequate contraception. In some cases, notably where a drug is clearly teratogenic, a protocol may need to require specific approaches to contraception.

17. One comment stated that sponsors must retain the right to exclude women of childbearing age from clinical trials involving compounds with the potential for teratogenic effects, unless

Congress enacts meaningful protection against liability. The comment based its concern on the potential liability of sponsors for any adverse effect on the offspring of study participants. The comment noted that many States permit a child adversely affected by a parent's medical decision, who has reached the age of majority, to sue for injuries alleged to have been caused by the drug. The comment also noted that, in some States, a parent's consent based on information in an FDA-approved warning does not preclude lawsuits by adult children.

FDA recognizes that, in some States, a child who has reached the age of majority or spouse may have the right to sue for injuries caused by a parent's medical decision to use a drug. To succeed in such a lawsuit, the child or spouse must show, among other things, that warnings about the use of the drug were inadequate or that consent was not fully informed.

FDA also recognizes that, in some States, parental consent based on FDA-approved warnings for marketed drugs might not preclude a child from filing a lawsuit. In States permitting such lawsuits, the courts have described FDA standards for such warnings as minimum requirements for disclosing risk information. Because manufacturers and sponsors have the ultimate responsibility to provide risk information to FDA as well as to consumers, in some States, FDA approval of warning statements for marketed drugs is evidence of the warning's adequacy but is not dispositive. These cases suggest that a warning might be inadequate when a sponsor or manufacturer obscures or withholds risk information from FDA, or delays submission of supplemental risk information obtained after the product was approved.

The sponsor or investigator, with IRB oversight, is responsible for providing risk information to subjects and obtaining informed consent from them. (See § 312.50 and 21 CFR 312.53(c)(1)(vi)(d); part 50 (21 CFR part 50) and part 56.) Few liability cases have been reported involving injuries from experimental drugs and even fewer involving such injuries to offspring. In those cases involving injuries to the offspring of mothers who ingested experimental drugs, the inadequacy of warnings, or the lack of informed consent, was an essential element of the lawsuit. (See *Craft v. Vanderbilt University*, 940 F. Supp. 1185 (M.D. Tenn. 1996); *Wetherill v.*

University of Chicago, 570 F. Supp. 1124 (N.D. Ill. 1983); *Mink v. University of Chicago*, 460 F. Supp. 713 (N.D. Ill. 1978); and *Diaz v. Hillsborough County Hospital Authority*, 165 F.R.D. 689 (M.D. Fla. 1996).) Although these cases involved research subjects who were pregnant women, they show that liability can be precluded when patients are informed adequately about a study and its risks. The women who brought these lawsuits claimed that they were not told that research was being conducted, much less asked for informed consent. The present rule is firmly grounded on informed consent and a fully informed patient.

The agency has found no reported case in which a sponsor or manufacturer of a drug was held liable when warnings were found to be adequate or the consent to be informed. In all of the strict liability cases involving marketed drug products, the adequacy of the warnings remains an essential element for avoiding liability. In determining the adequacy of a warning for prescription drug products, the standard generally applied is the drug maker's actual or constructive knowledge of the risk at the time the product was sold or distributed.

Considering all the relevant cases, the comment's concern about liability for injuries to offspring of study participants appears overstated. If anything, these cases show that the risk of liability for injuries to offspring resulting from their mother's ingestion of an experimental drug is remote. Sponsors and manufacturers can generally avoid liability by providing adequate warnings and obtaining fully informed consent.

This final rule applies to one narrow category of beneficial drugs, that is, experimental drugs being studied for their safety and effectiveness in treating life-threatening diseases or conditions. The rule also reduces the exposure to liability lawsuits by applying only to studies that seek subjects who are suffering from the life-threatening disease or condition at issue. The risk of liability is further minimized when the sponsor uses informed consent with careful study design, pregnancy screening techniques, and counseling about contraception and abstinence.

18. One comment expressed concern that informed consent alone may not be adequate to reduce the risk of injury to a participant and, thus, the risk of liability to a sponsor. Specifically,

the comment states that, in many situations, the full nature and extent of any potential reproductive toxicity may not be sufficiently characterized at the time of desired access to a given investigational therapy to allow IRB's, investigators, or potential study subjects to make a complete determination of any potential risk. To provide patients with complete risk and benefit information for certain developmental compounds or studies, consent forms would have to be worded in a way that could effectively discourage participation in these trials by the very population intended to benefit from the proposed regulation.

An inherent danger in the use of every experimental drug is that unknown safety risks may exist for human research subjects. The purpose of informed consent is to provide research volunteers with sufficient information to determine for themselves whether the risks are justified. Informed consent regulations require a sponsor, when appropriate, to describe the reasonably foreseeable risks, and currently unforeseeable risks, to the participant or to an embryo or fetus in the event the participant should become pregnant during the study (§ 50.26(b)(1)). That the disclosure of complete risk and benefit information might discourage participation is not a reason to withhold information or to preempt the opportunity to participate in a study. On the contrary, disclosure serves the interests of self-determination regarding a person's decision to participate in medical research and ensures informed decisionmaking as to whether the risks are indeed outweighed by the benefits.

19. One comment stated that exceptional circumstances may exist where the potential risk of the drug to the participant outweighs the potential benefit. As an example, the comment indicated that it may not be advisable to include treatment-naïve human immunodeficiency virus (HIV)-infected women with reproductive potential in clinical trials for a drug that has a high (or undetermined) risk to a fetus if there are other effective and safe agents in the same class available for use in these women.

HIV-infected women who are treatment-naïve should not be excluded from participating in clinical trials solely because of their reproductive potential. HIV-infected women should have a

choice, as should HIV-infected men, of enrolling in clinical trials, as long as there is a proper informed consent process that acknowledges the availability of safe and effective treatment options and, if the potential participants are sexually active, abstinence or contraception is used. After sponsor, FDA, and local IRB decisions on the protocol, the ultimate risk-benefit analysis in such circumstances is best left to the patient and the physician.

D. Increased Costs

20. Two comments supported the agency's position that the societal benefits outweigh the increased costs associated with the participation of women with reproductive potential who have a life-threatening disease in clinical trials. Both comments specifically highlighted the advantage of obtaining gender-specific data in this population.

Based on the analysis of economic impacts described in the proposed rule, the agency believes that the societal benefits outweigh the potential minimal additional costs because a considerable patient population (i.e., women with reproductive potential who have a life-threatening disease or condition) could receive a potentially beneficial new therapy (62 FR 49946 at 49953).

E. The Use of a Clinical Hold

21. The agency received divergent comments about the use of a clinical hold to achieve the objectives of the proposal. One comment stated a belief that it is appropriate for FDA to use its ability to place a clinical trial on hold if the sponsor excludes women for inappropriate reasons. However, another comment asserted that the use of a clinical hold in these circumstances is not consistent with the original intent of the clinical hold regulations and turns a clinical hold into a punitive measure.

A clinical hold is an order that FDA may issue to a sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation for the development of a new drug or biological product (§ 312.42). The agency has determined that it is appropriate to impose a clinical

hold on an investigation that categorically excludes women or men with reproductive potential who have a life-threatening disease or condition.

The imposition of a clinical hold under these amendments to § 312.42 is not punitive. The aim of these amendments is to ensure that women with reproductive potential who have a life-threatening disease or condition are not categorically excluded from participation in clinical trials. The rationale for this action, as discussed in the preamble to the proposed rule (62 FR 49946 at 49949 through 49951), is based on four factors: (1) FDA is committed to expanding access to and accelerating approval of new therapies for life-threatening diseases and conditions; (2) important ethical principles underlie the belief that neither gender should be excluded from early clinical trials involving a life-threatening disease or condition because of reproductive potential; (3) the mechanisms are in place, or are available, to protect individuals who participate in clinical trials from potential risks; and (4) FDA is committed to expanding the collection of gender-specific data on investigative therapies, especially for those populations who ultimately will be using the therapies. Furthermore, FDA intends to issue a clinical hold order as a last resort, only after the review division's attempt to discuss and satisfactorily resolve the matter with the sponsor (§ 312.42(c)). As explained in Center for Drug Evaluation and Research (CDER) internal policy statements, CDER experience is that most potential holds can be avoided through such discussion (CDER Manual of Policy and Procedure (MAPP) 6030.1).

In the preamble to the proposed rule (62 FR 49946 at 49951), FDA discussed its legal authority to issue this rule under section 505(i) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 355(i)). Since publication of the proposed rule, on November 21, 1997, the President signed into law the Food and Drug Administration Modernization Act of 1997 (the Modernization Act) (Public Law 105-115). Section 117 of the Modernization Act amends section 505(i) of the act to include specific provisions authorizing the imposition of a clinical hold on an investigation if “the drug involved represents an unreasonable risk to the safety of the persons who are the subjects of the clinical investigation * * * or * * * for such other reasons as the Secretary may by

regulation establish'' (section 505(i)(3)(B) of the act). The Modernization Act makes explicit the agency's authority to issue regulations for the imposition of a clinical hold for reasons other than unreasonable risks to the safety of the subjects involved in the investigation.

22. One comment noted a distinction between a clinical hold imposed for a regulatory purpose (e.g., because a sponsor has not made adequate provision for the inclusion of women with reproductive potential in a clinical trial) and one imposed due to safety concerns. The comment suggested that the agency establish a new set of regulations for this "regulatory clinical hold," rather than provide for it in the already-established clinical hold regulations.

FDA's regulations governing IND's are located in part 312 (21 CFR part 312), and the agency's clinical hold regulations are in § 312.42. FDA declines the suggestion to create a new set of regulations to accommodate these amendments because this change would serve no purpose and would be confusing, placing bases for clinical holds in two locations although the procedures for holds in both cases are identical. Furthermore, since President Clinton issued the "Regulatory Reinvention Initiative" memorandum on March 4, 1995, FDA has sought to consolidate its regulations and to eliminate duplicative ones. The creation of a new set of clinical hold regulations would be contrary to the objectives of regulatory reinvention.

23. One comment proposed safeguards to protect the interests of subjects already participating in a clinical trial and to ensure that a clinical hold is used only as a last resort. The comment proposed the following safeguards: (1) A limitation of the rule to those clinical trials that are intended to demonstrate effectiveness and (2) procedures to ensure a dialogue between the sponsor and the agency to help avoid the imposition of the clinical hold. The comment recommended that when a clinical hold is issued for inadequate participation of women in the trial, procedural safeguards should include: (1) The concurrence of the Center Director after personal consultation between the Division Director and the sponsor; (2) communication of the reason for the hold to the sponsor in writing within 10 days of the imposition of a clinical hold; and (3) review by the Clinical Hold Review Committee at the first meeting following the hold.

The comment states that under this rule, a clinical hold may be issued for inadequate participation of women in a clinical trial. This statement erroneously implies that the rule imposes requirements to enroll or recruit a specific number of women in trials. To the contrary, the rule prohibits the exclusion of women with reproductive potential but does not require a quota or specific number of women for any trial.

The agency declines the suggestion to limit the scope of the rule to those clinical trials that are intended to demonstrate effectiveness. As explained in the preamble to the proposed rule (62 FR 49946 at 49949), many early clinical studies involving life-threatening diseases offer the potential for therapeutic benefit, especially when participation in an early clinical study is a prerequisite for enrollment in later studies. FDA has concluded that all trials involving patients with life-threatening diseases and conditions should, for purposes of this rule, be considered to have therapeutic potential. This rule, therefore, applies to studies in any phase of a clinical investigation that enroll participants with a life-threatening disease or condition.

The agency's clinical hold regulations provide a process for discussion between a sponsor and FDA about deficiencies in an investigation to ensure that a clinical hold is imposed as a measure of last resort. Whenever FDA concludes that a deficiency exists in a clinical investigation that may be grounds for the imposition of a clinical hold, FDA will, unless patients are exposed to immediate and serious risk, attempt to discuss and satisfactorily resolve the matter with the sponsor before issuing the clinical hold order (§ 312.42(c)).

Under FDA regulations, the Division Director that is responsible for reviewing the application for the underlying drug product has the authority to determine whether to impose a clinical hold (§ 312.42(d)). The agency does not find that concurrence by the Center Director is necessary to ensure that a clinical hold is imposed only as a last resort because, as discussed above, the agency's regulations and internal procedures already provide for discussion between the sponsor and the agency concerning the need for the clinical hold. Division directors in CDER and the Center for

Biologics Evaluation and Research (CBER) have the authority to ensure that agency personnel follow these regulations and procedures.

FDA regulations state that the agency will communicate to the sponsor in writing the reasons for a clinical hold as soon as possible, and no more than 30 days after imposing the hold (§ 312.42(d)). A clinical hold is usually imposed only after discussion between FDA and a sponsor. Because the Division Director, or designee, generally provides a brief explanation of the reasons for the hold by telephone at the time the clinical hold is ordered, the agency finds it unnecessary to shorten the 30-day requirement for a written explanation.

CDER and CBER have established committees to review clinical holds and promote consistency throughout the Centers in issuing clinical holds. Under CDER policy, the CDER Clinical Holds Peer Review Committee meets quarterly to review all commercial IND clinical holds issued during the previous quarter (CDER MAPP 6030.1). The CBER Clinical Hold Oversight Committee reviews selected clinical holds that have been issued. The procedures for these committees will apply to clinical holds imposed by CDER or CBER under this rule.

24. Two comments indicated that this use of a clinical hold is not the optimal mechanism to achieve the agency's objectives and may threaten other agency goals (e.g., expediting the development of innovative therapies to treat life-threatening diseases and conditions in both men and women). One comment further noted that the best way to ensure that women and men of reproductive potential are able to participate in clinical trials is to address the issue during the development of the protocol for the trial early in the IND process. The comment recommended that a plan be developed in the IND process for including women of reproductive potential in clinical studies or articulating a clear rationale for their exclusion. The sponsor and the agency should agree on the plan as part of the IND with compliance tied to the plan and progress reported in routine annual reports to the IND.

Although developing data bases that include both men and women is an important goal, this rule does not address the content of an NDA or biologics license application (BLA) data set. Rather,

this rule seeks to prevent exclusions of people suffering from life-threatening conditions or diseases from participation in trials based on reproductive potential.

Overall protocol development is addressed under several regulatory programs for the development and review of products that are intended to treat life-threatening diseases or conditions. The agency recognizes that agreement between a sponsor and FDA on a protocol for a clinical trial is an important step towards ensuring that women with reproductive potential who have a life-threatening disease or condition are not excluded from the clinical trial. Under the agency's regulations at §§ 312.80 through 312.88, sponsors are encouraged to work with the agency during the development of drugs intended to treat life-threatening and severely debilitating illnesses. Sponsors may ask to meet with FDA early in the drug development process to review and reach agreement on the design of necessary preclinical and clinical studies (§ 312.82). Such meetings may take place prior to the submission of the IND or at the end of phase 1. Furthermore, under section 112 of the Modernization Act, the agency has developed procedures to facilitate the development and expedite the review of products that are intended to treat serious or life-threatening conditions and demonstrate the potential to address an unmet medical need. Such procedures, described in the FDA guidance entitled "Fast Track Drug Development Programs—Designation, Development, and Application Review" (October 1998), encourage appropriately timed meetings and regular contact between sponsors and FDA.

Section 119(a) of the Modernization Act directs FDA to work towards, and achieve, agreement with sponsors and applicants on the design and size of clinical trials intended to form the primary basis of an effectiveness claim in an NDA or BLA. In conjunction with the reauthorization of the Prescription Drug User Fee Act in November 1997, FDA agreed to specific performance goals for the management of activities associated with the development and approval of products in human drug applications that are defined in section 735(1) of the act (21 U.S.C. 379g(1)). Under the goals, FDA will, upon request by a sponsor, evaluate certain protocols and issues relating to the protocols to assess whether their design is adequate to meet scientific and regulatory

requirements identified by the sponsor. One type of protocol that is eligible for this special protocol assessment is a clinical protocol for a phase 3 trial whose data will form the primary basis for an efficacy claim. Section 119(a) of the Modernization Act and the performance goals recognize the importance of early agency review and agreement with sponsors regarding protocols for clinical trials.

Sponsors are required to submit information regarding the progress of IND's in their annual reports to the agency (§ 312.33). Any specific information regarding a clinical protocol agreement should be included in the annual report. Furthermore, sponsors of clinical studies for drug and biologic products are now required to tabulate in annual reports the numbers of subjects enrolled in the trial, specifying gender and other demographic subgroups (§ 312.33) (see 63 FR 6854).

F. International Issues

25. FDA received two comments concerning the effect of the regulation on international drug development. One comment questioned how the regulation will affect compliance with the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) "Draft Guideline on the Timing of Nonclinical Studies for the Conduct of Human Clinical Trials for Pharmaceuticals." The comment stated that the impact of the rule on global drug development remains unclear and questioned whether data collected from trials conducted under the rule would be acceptable to the regulatory agencies in Europe or Japan. Another comment raised the possibility of regulatory difficulties in including women of reproductive potential in some early studies when those studies are subject to regulation by agencies in other countries. The comment urged FDA to consider the effects of the proposed rule on multicountry studies.

The final rule is consistent with ICH initiatives. In July 1997, FDA issued a final ICH guidance entitled "M3 Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals" (ICH M3 guidance) (published in 62 FR 62922, November 25, 1997). The ICH M3 guidance, which supersedes the draft guideline cited in the comment, notes that there are

regional differences in the timing of reproductive toxicity studies to support the inclusion of women with reproductive potential in clinical trials for all pharmaceuticals. As described in the ICH M3 guidance, women with reproductive potential may be included in early, carefully monitored studies in the United States without reproduction toxicity studies provided appropriate precautions are taken to minimize risk. Such precautions include pregnancy testing, use of a highly effective method of birth control, and entry after a confirmed menstrual period. Continued testing and monitoring during the trial should be sufficient to ensure compliance with the measures for avoiding pregnancy during the period of drug exposure (which may exceed the length of the study). To support this approach, informed consent should include any known pertinent information related to reproductive toxicity, such as a general assessment of potential toxicity of pharmaceuticals with related structures or pharmacological effects. If no relevant information is available, the informed consent should clearly note the potential for risk (ICH M3 guidance, p. 7).

In multicountry studies, provided that there is not a categorical exclusion based on reproductive potential in the United States, FDA does not intend to impose a hold for such exclusions on studies in foreign sites. Foreign data with such exclusions may be submitted to the agency.

G. HIV/Acquired Immune Deficiency Syndrome (AIDS)

26. One comment discussed the Center for Disease Control's reports of a steady decline in AIDS incidence and mortality rates in the United States since 1993 and highlighted the disparities related to women. The comment noted that the number of AIDS deaths in 1996 declined among all racial/ethnic groups but increased 3 percent among women and among those who acquired the infection through heterosexual contact. The comment emphasized the treatment and prevention challenges affecting HIV-infected women, highlighted the need for gender-specific data, and advocated the enrollment of women in clinical trials in numbers equivalent to the prevalence of women with AIDS in America.

As discussed in the preamble to the proposed rule (62 FR 49946 at 49950 and 49951), FDA is committed to expanding the collection of gender-specific data on investigative therapies,

especially for those populations who are likely to use an investigational agent once it is marketed. Because many of the women who are affected by HIV and AIDS are women with reproductive potential, this rule will prevent their exclusion from participation in clinical trials for such diseases solely because of a perceived risk or potential risk of reproductive or developmental toxicity.

The Division of Antiviral Drug Products in CDER and other components in CDER and CBER that review HIV/AIDS-related products encourage sponsors to include women of all age groups early in the drug development process and support the concept of allowing each eligible female participant to make her own informed decision regarding the risks and benefits of participating in a trial.

The comment suggested that women be enrolled in clinical trials for AIDS therapies in numbers equivalent to the prevalence of women with AIDS in America. The comment is outside the scope of this rule. The rule does not require that particular numbers of women be enrolled in trials for investigational therapies. The rule only prohibits the exclusion of women with reproductive potential from eligibility for a clinical trial.

27. One comment indicated that the proposal is a broad-based solution to a focused problem that the agency has identified within a single drug class—antiviral drugs.

Although FDA prepared this proposal largely in response to recommendations made by the National Task Force on AIDS Drug Development and the Presidential Advisory Council on HIV/AIDS, the recommendations are applicable to all life-threatening diseases and conditions, and the agency has concluded that this problem is a general one. Additionally, when conducting its cost analysis, the agency used a protocol data base that included information from four CDER review divisions. Of the 43 protocols involving life-threatening diseases or conditions that were identified as having precluded the opportunity for women with reproductive potential to participate in trials, 28 percent were from the Division of Antiviral Drug Products, 67 percent were from the Division of Cardio-Renal Drug Products, and the remaining 5 percent were from the Division of Medical Imaging, Surgical, and Dental Drug Products and the Pilot Drug Evaluation Staff. The project

did not include representation of all divisions in CDER and CBER. However, it was assumed that the available data were representative of all CDER and CBER review divisions regarding the exclusion of women with reproductive potential.

IV. Analysis of Impacts

FDA has examined the impacts of the final rule under Executive Order 12866 and the Regulatory Flexibility Act (Public Law 96-354). Executive Order 12866 directs agencies to assess all costs and benefits or available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages). Under the Regulatory Flexibility Act (5 U.S.C. 601-612), unless an agency certifies that a rule will not have a significant economic impact on small entities, the agency must analyze regulatory options that would minimize the impact of the rule on small entities. Title II of the Unfunded Mandates Reform Act (Public Law 104-7) (in section 202) requires that agencies prepare an assessment of anticipated costs and benefits before proposing any rule that may result in an expenditure in any 1 year by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100 million or more (adjusted annually for inflation).

The agency has reviewed this rule and has determined that it is consistent with the regulatory philosophy and principles identified in Executive Order 12866, and in these two statutes. In addition, the final rule is not a significant regulatory action as defined by the Executive Order and so is not subject to review under the Executive Order. With respect to the Regulatory Flexibility Act, the agency certifies that the rule will not have a significant effect on a substantial number or small entities. Because the final rule does not impose any mandates on State, local, or tribal governments, or the private sector that will result in a 1-year expenditure of \$100 million or more, FDA is not required to perform a cost-benefit analysis under the Unfunded Mandates Reform Act.

A. Costs

The Costs section of the Analysis of Impacts in the proposed rule (62 FR 49952) remains essentially unchanged and is not repeated here. However, two items require additional comment.

None of the cost estimates in the proposed rule were corrected for the incidence of pregnant women having diseases under study (but not having been included in the studies). Hence, the cost estimates discussed in the proposed rule were overstated. The agency believes that the effect of this overstatement is relatively insignificant.

The agency is aware of industry's concerns about liability exposure associated with the inclusion of women with reproductive potential in clinical trials and the potential for harm to offspring. Although there are cases of injury to offspring of mothers who ingested experimental drugs, the inadequacy of warnings or the lack of informed consent has been an essential element of such lawsuits. The agency is not aware of any reported case in which a sponsor of an investigational drug was held liable for injuries to offspring when the sponsor provided adequate warnings and obtained fully informed consent. Therefore, the agency assumes that this rule adds nothing to current liability costs under existing law.

B. Small Entities

The analysis in the proposed rule identified protocols sponsored by small businesses. The largest additional pregnancy testing cost incurred by a small business in the reviewed protocols under the rule was \$990. Projected across all CDER and CBER review divisions and annualized, FDA expects no more than 9 protocol submissions per year from small businesses that might incur increased costs. Few small firms are likely to be affected in any given year, and most of these firms would incur no significant additional costs. Therefore, under the Regulatory Flexibility Act, the Commissioner of Food and Drugs certifies that this rule will not have a significant effect on a substantial number of small entities.

V. Environmental Impact

The agency has determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VI. Paperwork Reduction Act of 1995

This final rule contains no collections of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

VII. Federalism

FDA has analyzed this final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the rule does not contain policies that have substantial direct effects on the States, on the relationship between National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the agency has concluded that the rule does not contain policies that have federalism implications as defined in the order and, consequently, a federalism summary impact statement is not required.

List of Subjects in 21 CFR Part 312

Drugs, Exports, Imports, Investigations, Labeling, Medical research, Reporting and recordkeeping requirements, Safety.

Therefore, under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 312 is amended as follows:

PART 312—INVESTIGATIONAL NEW DRUG APPLICATION

1. The authority citation for 21 CFR part 312 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 371; 42 U.S.C. 262.

2. Section 312.42 is amended by adding new paragraph (b)(1)(v) and by revising paragraph (b)(2)(i) to read as follows:

§ 312.42 Clinical holds and requests for modification.

* * * * *

(b) * * *

(1) * * *

(v) The IND is for the study of an investigational drug intended to treat a life-threatening disease or condition that affects both genders, and men or women with reproductive potential who have the disease or condition being studied are excluded from eligibility because of a risk or potential risk from use of the investigational drug of reproductive toxicity (i.e., affecting reproductive organs) or developmental toxicity (i.e., affecting potential offspring). The phrase “women with reproductive potential” does not include pregnant women. For purposes of this paragraph, “life-threatening illnesses or diseases” are defined as “diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted.” The clinical hold would not apply under this paragraph to clinical studies conducted:

(A) Under special circumstances, such as studies pertinent only to one gender (e.g., studies evaluating the excretion of a drug in semen or the effects on menstrual function);

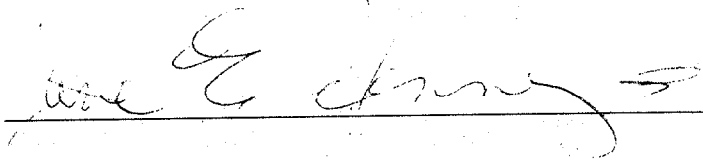
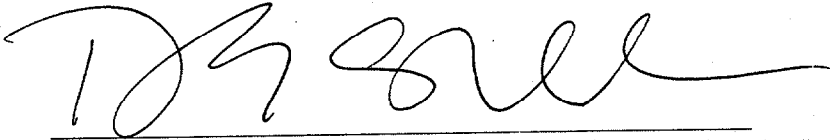
(B) Only in men or women, as long as a study that does not exclude members of the other gender with reproductive potential is being conducted concurrently, has been conducted, or will take place within a reasonable time agreed upon by the agency; or

(C) Only in subjects who do not suffer from the disease or condition for which the drug is being studied.

(2) * * *

(i) Any of the conditions in paragraphs (b)(1)(i) through (b)(1)(v) of this section apply; or

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Dated: MAY 24 2000**Jane E. Henney,***Commissioner of Food and Drugs.***Donna E. Shalala,***Secretary of Health and Human Services.*

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